## Appendix 4

## Alignment of dengue virus polyproteins

DEN4	1	MNQRKKVVRPPFNMLKRERNRVSTPQGLVKRFSTGLFSGKGPLRMVLAF	49
DEN1-WP	1	MNNQRKKTGRPSFNMLKRARNRVSTVSQLAKRFSKGLLSGQGPMKLVMAF	50
DEN2-NGC	1	MNNQRKKARNTPFNMLKRERNRVSTVQQLTKRFSLGMLQGRGPLKLFMAL	50
DEN3-H87	1	MNNORKKTGKPSINMLKRVRNRVSTGSOLAKRFSRGLLNGOGPMKLVMAF	50
	_	**** **** * **** * * * * * * * * * * * *	
DEN4	50	ITFLRVLSIPPTAGILKRWGOLKKNKAIKILIGFRKEIGRMLNILNGRKR	99
		IAFLRFLAIPPTAGILARWGSFKKNGAIKVLRGFKKEISNMLNIMNRRKR	100
DEN1-WP			
DEN2-NGC		VAFLRFLTIPPTAGILKRWGTIKKSKAINVLRGFRKEIGRMLNILNRRRR	100
DEN3-H87	51	IAFLRFLAIPPTAGVLARWGTFKKSGAIKVLKGFKKEISNMLSIINKRKK	100
		*** *.*****.* *** ** .* **.*** ** *.* *	
DEN4		STITLLCLIPTVMAFSLSTRDGEPLMIVAKHERGRPLLFKTTEGINKCTL	149
DEN1-WP		SVTMLLMLLPTALAFHLTTRGGEPHMIVSKQERGKSLLFKTSAGVNMCTL	150
DEN2-NGC	101	TAGMIIMLIPTVMAFHLTTRNGEPHMIVSRQEKGKSLLFKTEDGVNMCTL	150
DEN3-H87	101	TSLCLMMMLPATLAFHLTSRDGEPRMIVGKNERGKSLLFKTASGINMCTL	150
		*** ** *** . *.*. **** *.* ***	
DEN4	150	IAMDLGEMCEDTVTYKCPLLVNTEPEDIDCWCNLTSTWVMYGTCTQSGER	199
DEN1-WP	151	IAMDLGELCEDTMTYKCPRITETEPDDVDCWCNATETWVTYGTCSQTGEH	200
DEN2-NGC	151	MAMDLGELCEDTITYKCPFLRONEPEDIDCWCNSTSTWVTYGTCTTTGEH	200
DEN3-H87		IAMDLGEMCDDTVTYKCPHITEVEPEDIDCWCNLTSTWVTYGTCNQAGEH	200
DEN3-110 /	131	****** * * * * * * * * * * * * * * * *	200
		.,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
DEN4	200	RREKRSVALTPHSGMGLETRAETWMSSEGAWKHAQRVESWILRNPGFALL	249
DEN1-WP		RRDKRSVALAPHVGLGLETRTETWMSSEGAWKQIQKVETWALRHPGFTVI	250
DEN2-NGC		RREKRSVALVPHVGMGLETRTETWMSSEGAWKHAORIETWILRHPGFTIM	250
	-	~	250
DEN3-H87	201	RRDKRSVALAPHVGMGLDTRTQTWMSAEGAWRQVEKVETWALRHPGFTIL **.***** ** *.**.****.* ***.* ***.**.*	250
		**,***** ** *,**,**,.***,.***,,	
DEN4	250	AGFMAYMIGOTGIORTVFFVLMMLVAPSYGMRCVGVGNRDFVEGVSGGAW	299
			300
DEN1-WP		ALFLAHAIGTSITQKGIIFILLMLVTPSMAMRCVGIGNRDFVEGLSGATW	
DEN2-NGC	_	AAILAYTIGTTHFQRALIFILLTAVAPSMTMRCIGISNRDFVEGVSGGSW	300
DEN3-H87	251	ALFLAHYIGTSLTQKVVIFILLMLVTPSMTMRCVGVGNRDFVEGLSGATW	300
		* .* ** . * *.*. *.** ***.*. ******.** .*	
DEN4	200	VDLVLEHGGCVTTMAOGKPTLDFELTKTTAKEVALLRTYCIEASISNITT	349
DEN4			
DEN1-WP		VDVVLEHGSCVTTMAKDKPTLDIELLKTEVTNPAVLRKLCIEAKISNTTT	350
DEN2-NGC		VDIVLEHGSCVTTMAKNKPTLDFELIKTEAKQPATLRKYCIEAKLTNTTT	350
DEN3-H87	301	VDVVLEHGGCVTTMAKNKPTLDIELQKTEATQLATLRKLCIEGKITNITT	350
		**.**** *****. **** * * * * * * * * ** **	
DDN4	250	AMD ADMOGRAVI VERODOOVI ADDDUNDRAWAYAAA EAVAATAMAA VEC	200
DEN4		ATRCPTQGEPYLKEEQDQQYICRRDVVDRGWGNGCGLFGKGGVVTCAKFS	399
DEN1-WP		DSRCPTQGEATLVEEQDTNFVCRRTFVDRGWGNGCGLFGKGSLITCAKFK	400
DEN2-NGC		DSRCPTQGEPSLNEEQDKRFVCKHSMVDRGWGNGCGLFGKGGIVTCAMFT	400
DEN3-H87	351	DSRCPTQGEAILPEEQDQNYVCKHTYVDRGWGNGCGLFGKGSLVTCAKFQ	400
		.***** * ***** ************** *	

DEN4 DEN1-WP DEN2-NGC DEN3-H87	401 401	CSGKITGNLVQIENLEYTVVVTVHNGDTHAVGNDTSNHGVTAMITPRSPS CVTKLEGKIVQYENLKYSVIVTVHTGDQHQVGNETTEHGTTATITPQAPT CKKNMKGKVVQPENLEYTIVITPHSGEEHAVGNDTGKHGKEIKITPQSSI CLESIEGKVVQHENLKYTVIITVHTGDQHQVGNETQGVTAEITSQAST * . * . * * * * * * * * * * * * * * * *	449 450 450 448
DEN4	450	VEVKLPDYGELTLDCEPRSGIDFNEMILMKMKKKTWLVHKQWFLDLPLPW	499
DEN1-WP	451	SEIQLTDYGALTLDCSPRTGLDFNEMVLLTMEKKSWLVHKQWFLDLPLPW	500
DEN2-NGC	451	TEAELTGYGTVTMECSPRTGLDFNEMVLLQMENKAWLVHRQWFLDLPLPW	500
DEN3-H87	449	AEAILPEYGTLGLECSPRTGLDFNEMILLTMKNKAWMVHRQWFFDLPLPW	498
		* * ** * ** . * . * . * . * . * .	
DEN4	500	TAGADTSEVHWNYKERMVTFKVPHAKRQDVTVLGSQEGAMHSALAGATEV	549
DEN1-WP	501	TSGASTSQETWNRQDLLVTFKTAHAKKQEVVVLGSQEGAMHTALTGATEI	550
DEN2-NGC	501	LPGADTQGSNWIQKETLVTFKNPHAKKQDVVVLGSQEGAMHTALTGATEI	550
DEN3-H87	499	TSGATTKTPTWNRKELLVTFKNAHAKKQEVVVLGSQEGAMHTALTGATEI	548
		** *	
DEN4	550	DSGDGNHMFAGHLKCKVRMEKLRIKGMSYTMCSGKFSIDKEMAETOHGTT	599
DEN1-WP	551	OTSGTTTIFAGHLKCRLKMDKLTLKGMSYVMCTGSFKLEKEVAETQHGTV	600
DEN2-NGC	551	QMSSGNLLFTGHLKCRLRMDKLQLKGMSYSMCTGKFKVVKEIAETQHGTI	600
DEN3-H87	549	QTSGGTSIFAGHLKCRLKMDKLKLKGMSYAMCLNTFVLKKEVSETQHGTI	598
		* . * * * * * . * . * . * . *	
DEN4	600	VVKVKYEGAGAPCKVPIEIRDVNKEKVVGRIISSTPLAENTNSVTNIELE	649
DEN1-WP	601	LVOVKYEGTDAPCKIPFSSQDEKGVTQNGRLITANPIVTDKEKPVNIEAE	650
DEN2-NGC	601	VIRVOYEGDGSPCKIPFEIMDLEKRHVLGRLITVNPIVTEKDSPVNIEAE	650
DEN3-H87	599	LIKVEYKGEDAPCKIPFSTEDGQGKAHNGRLITANPVVTKKEEPVNIEAE	648
		* * * .***.* * **.*. **.	
DEN4	650	PPFGDSYIVIGVGNSALTLHWFRKGSSIGKMFESTYRGAKRMAILGETAW	699
DEN1-WP	651	PPFGESYIVVGAGEKALKLSWFKKGSSIGKMFEATARGARRMAILGDTAW	700
DEN2-NGC	651	PPFGDSYIIIGVEPGOLKLNWFKKGSSIGOMIETTMRGAKRMAILGDTAW	700
DEN3-H87	649	PPFGESNIVIGIGDKALKINWYRKGSSIGKMFEATARGARRMAILGDTAW	698
		****.* ** * . ******* *.* *.* ***.***	
DEN4	700	DFGSVGGLFTSLGKAVHOVFGSVYTTMFGGVSWMIRILIGFLVLWIGTNS	749
DEN1-WP		DFGSIGGVFTSVGKLIHOIFGTAYGVLFSGVSWTMKIGIGILLTWLGLNS	750
DEN2-NGC		DFGSLGGVFTSIGKALHQVFGAIYGAAFSGVSWTMKILIGVIITWIGMNS	750
DEN3-H87		DFGSVGGVLNSLGKMVHOIFGSAYTALFSGVSWIMKIGIGVLLTWIGLNS	748
		****.***.**.**. * ***** ** *.*	
DEN4	750	RNTSMAMTCIAVGGITLFLGFTVQADMGCVASWSGKELKCGSGIFVVDNV	799
DEN1-WP		RSTSLSMTCIAVGMVTLYLGVMVQADSGCVINWKGRELKCGSGIFVTNEV	800
DEN2-NGC		RSTSLSVSLVLVGVVTLYLGVMVOADSGCVVSWKNKELKCGSGIFITDNV	800
DEN3-H87	_	KNTSMSFSCIAIGIITLYLGVVVQADMGCVINWKGKELKCGSGIFVTNEV	798
		. ** * . ** *	,
DEN4	800	HTWTEQYKFQPESPARLASAILNAHKDGVCGIRSTTRLENVMWKQITNEL	849
DEN1-WP		HTWTEQYKFQADSPKRLSAAIGKAWEEGVCGIRSATRLENIMWKQISNEL	850
DEN2-NGC		HTWTEQYKFQPESPSKLASAIQKAHEEGICGIRSVTRLENLMWKQITPEL	850
DEN3-H87		HTWTEOYKFOADSPKRVATAIAGAWENGVCGIRSTTRMENLLWKQIANEL	848
		****** .**** * *.**** **.**. **	

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850 NYVLWEGGHDLTVVAGDVKGVLTKGKRALTPPVSDLKYSWKTWGKAKIFT
DEN4
          851 NHILLENDMKFTVVVGDVSGILAQGKKMIRPQPMEHKYSWKSWGKAKIIG 900
DEN1-WP
DEN2-NGC
          851 NHILSENEVKLTIMTGDIKGIMOAGKRSLQPQPTELKYSWKTWGKAKMLS
                                                                900
          849 NYILWENDIKLTVVVGDITGVLEOGKRTLTPQPMELKYSWKTWGLAKIVT
                                                                898
DEN3-H87
                         *.. **. *.. **. . * . *****.** **.
              * * * * .
          900 PEARNSTFLIDGPDTSECPNERRAWNSLEVEDYGFGMFTTNIWMKFREGS
                                                                949
DEN4
DEN1-WP
          901 ADVQNTTFIIDGPNTPECPDNQRAWNIWEVEDYGFGIFTTNIWLKLRDSY
                                                                950
          901 TESHNOTFLIDGPETAECPNTNRAWNSLEVEDYGFGVFTTNIWLKLREKQ
                                                                950
DEN2-NGC
          899 AETONSSFIIDGPSTPECPSASRAWNVWEVEDYGFGVFTTNIWLKLREVY
                                                                948
DEN3-H87
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DEN4
          950 SEVCDHRLMSAAIKDQKAVHADMGYWIESSKNQTWQIEKASLIEVKTCLW 999
          951 TOVCDHRLMSAAIKDSKAVHADMGYWIESEKNETWKLARASFIEVKTCIW 1000
DEN1-WP
         951 DVFCDSKLMSAAIKDNRAVHADMGYWIESALNDTWKIEKASFIEVKSCHW 1000
DEN2 - NGC
          949 TOLCDHRLMSAAVKDERAVHADMGYWIESOKNGSWKLEKASLIEVKTCTW 998
DEN3-H87
                 ** **** ** ******** * * * * *** * *
         1000 PKTHTLWSNGVLESQMLIPKSYAGPFSQHNYRQGYATQTVGPWHLGKLEI 1049
DEN4
         1001 PKSHTLWSNGVLESEMIIPKIYGGPISQHNYRPGYFTQTAGPWHLGKLEL 1050
DEN1-WP
DEN2-NGC 1001 PKSHTLWSNGVLESEMIIPKNFAGPVSOHNYRPGYHTOTAGPWHLGKLEM 1050
         999 PKSHTLWSNGVLESDMIIPKSLAGPISQHNHRPGYHTQTAGPWHLGKLEL 1048
DEN3-H87
              ** | * * * * * * * * * | * * * * |
                                   ** *** * ** *** *****
         1050 DFGECPGTTVTIOEDCDHRGPSLRTTTASGKLVTOWCCRSCTMPPLRFLG 1099
DEN4
         1051 DFDLCEGTTVVVDEHCGNRGPSLRTTTVTGKTIHEWCCRSCTLPPLRFKG 1100
DEN1-WP
DEN2-NGC 1051 DFDFCEGTTVVVTEDCGNRGPSLRTTTASGKLITEWCCRSCTLPPLRYRG 1100
DEN3-H87
         1049 DFNYCEGTTVVISENCGTRGPSLRTTTVSGKLIHEWCCRSCTLPPLRYMG 1098
              ** * *** * * ****** ** ****** *
         1100 EDGCWYGMEIRPLSEKEENMVKSQVTAGQGTSETFSMGLLCLTLFVEECL 1149
DEN4
DEN1-WP
         1101 EDGCWYGMEIRPVKEKEENLVKSMVSAGSGEVDSFSLGLLCISIMIEEVM 1150
DEN2-NGC 1101 EDGCWYGMEIRPLKEKEENLVNSLVTAGHGQIDNFSLGVLGMALFLEEML 1150
DEN3-H87 1099 EDGCWYGMEIRPINEKEENMVKSLASAGSGKVDNFTMGVLCLAILFEEVM 1148
              ********* ***** * .** * . *..*.* ... ** .
DEN4
         1150 RRRVTRKHMILVVVITLCAIILGGLTWMDLLRALIMLGDTMSGRIG-GQI 1198
         1151 RSRWSRKMLMTGTLAVFLLLTMGQLTWNDLIRLCIMVGANASDKMGMGTT 1200
DEN1-WP
DEN2-NGC 1151 RTRVGTKHAILLVAVSFVTLITGNMSFRDLGRVMVMVGATMTDDIGMGVT 1200
         1149 RGKFGKKHMIAGVLFTFVLLLSGQITWRGMAHTLIMIGSNASDRMGMGVT 1198
DEN3-H87
                                DEN4
         1199 HLAIMAVFKMSPGYVLGVFLRKLTSRETALMVIGMAMTTVLSIPHDLMEL 1248
         1201 YLALMATFRMRPMFAVGLLFRRLTSREVLLLTVGLSLVASVELPNSLEEL 1250
DEN1-WP
DEN2-NGC 1201 YLALLAAFKVRPTFAAGLLLRKLTSKELMMTTIGIVLLSQSTIPETILEL 1250
         1199 YLALIATFKIQPFLALGFFLRKLTSRENLLLGVGLAMAATLRLPEDIEQM 1248
DEN3-H87
               **..* *.. *
                            1249 IDGISLGLILLKIVTOFDNTOVGTLALSLTFIRSTMPLVMAWRTIMAVLF 1298
DEN4
DEN1-WP
         1251 GDGLAMGIMMLKLLTDFOSHOLWATLLSLTFVKTTFSLHYAWKTMAMILS 1300
DEN2-NGC 1251 TDALALGMMVLKMVRKMEKYQLAVTIMAILCVPNAVILQNAWKVSCTILA 1300
DEN3-H87 1249 ANGIALGLMALKLITQFETYQLWTALVSLTCSNTIFTLTVAWRTATLILA 1298
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1299 VVTLIPLCRTSCLOKOSHWVEITALILGAQALPVYLMTLMKGASRRSWPL 1348
DEN4
         1301 IVSLFPLCLSTTSQK-TTWLPVLGSLGCKPLTMFLITENKIWGRKSWPL 1349
DEN1-WP
DEN2-NGC 1301 VVSVSPLFLTSSQQK-ADWIPLALTIKGLNPTAIFLTTLSRTNKKRSWPL 1349
DEN3-H87 1299 GISLLPVCOSSSMRK-TDWLPMTVAAMGVPPLPLFIFSLKDTLKRRSWPL 1347
               ... *. ... .* . *. .
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         1349 NEGIMAVGLVSLLGSALLKNDVPLAGPMVAGGLLLAAYVMSGSSADLSLE 1398
DEN4
DEN1-WP
         1350 NEGIMAVGIVSILLSSLLKNDVPLAGPLIAGGMLIACYVISGSSADLSLE 1399
DEN2-NGC 1350 NEAIMAVGMVSILASSLLKNDIPMTGPLVAGGLLTVCYVLTGRSADLELE 1399
DEN3-H87 1348 NEGVMAVGLVSILASSLLRNDVPMAGPLVAGGLLIACYVITGTSADLTVE 1397
              DEN4
         1399 KAANVQWDEMADITGSSPIIEVKQDEDGSFSIRDVEETNMITLLVKLALI 1448
         1400 KAAEVSWEEEAEHSGASHNILVEVQDDGTMKIKDEERDDTLTILLKATLL 1449
DEN1-WP
DEN2-NGC 1400 RAADVKWEDQAEISGSSPILSITISEDGSMSIKNEEEEQTLTILIRTGLL 1449
DEN3-H87 1398 KAADVTWEEEAEQTGVSHNLMITVDDDGTMRIKDDETENILTVLLKTALL 1447
              .** * *.. *. .* * . . . . . . . . *. *.
                                                    .*.*.. *.
         1449 TVSGLYPLAIPVTMTLWYMWQVKTQRSGALWDVPSPAATKKAALSEGVYR 1498
DEN4
         1450 AISGVYPMSIPATLFVWYFWQKKKQRSGVLWDTPSPPEVERAVLDDGIYR 1499
DEN1-WP
DEN2-NGC 1450 VISGLFPVSIPITAAAWYLWEVKKQRAGVLWDVPSPPPVGKAELEDGAYR 1499
DEN3-H87 1448 IVSGIFPYSIPATMLVWHTWQKQTQRSGVLWDVPSPPETQKAELEEGVYR 1497
               .**..* .** * * * . . **.* ***
         1499 IMORGLFGKTOVGVGIHMEGVFHTMWHVTRGSVICHETGRLEPSWADVRN 1548
DEN4
         1500 ILORGLLGRSOVGVGVFOEGVFHTMWHVTRGAVLMYOGKRLEPSWASVKK 1549
DEN1-WP
DEN2-NGC
         1500 IKOKGILGYSQIGAGVYKEGTFHTMWHVTRGAVLMHKGKRIEPSWADVKK 1549
DEN3-H87
         1498 IKOOGIFGKTOVGVGVGVEGVFHTMWHVTRGAVLTHNGKRLEPNWASVKK 1547
              * * * * * * .
         1549 DMISYGGGWRLGDKWDKEEDVQVLAIEPGKNPKHVQTKPGLFKTLTGEIG 1598
DEN4
DEN1-WP
         1550 DLISYGGGWRFOGSWNAGEEVOVIAVEPGKNPKNVOTAPGTFKTPEGEVG 1599
DEN2-NGC 1550 DLISYGGGWKLEGEWKEGEEVQVLALEPGKNPRAVQTKPGLFKTNAGTIG 1599
DEN3-H87 1548 DLISYGGGWRLSAQWQKGEEVQVIAVEPGKNPKNFQTMPGIFQTTTGEIG 1597
                              *.***.*.*****. ** ** *.*
              * ******
DEN4
         1599 AVTLDFKPGTSGSPIINRKGKVIGLYGNGVVTKSGDYVSAITOAERIGEP 1648
DEN1-WP
         1600 AIALDFKPGTSGSPIVNREGKIVGLYGNGVVTTSGTYVSAIAQAKASQEG 1649
         1600 AVSLDFSPGTSGSPIIDKKGKVVGLYGNGVVTRSGAYVSAIAQTEKSIED 1649
DEN2-NGC
         1598 AIALDFKPGTSGSPIINREGKVVGLYGNGVVTKNGGYVSGIAQTNAEPDG 1647
DEN3-H87
              DEN4
         1649 -DYEVDEDIFRKKRLTIMDLHPGAGKTKRILPSIVREALKRRLRTLILAP 1697
         1650 PLPEIEDEVFRKRNLTIMDLHPGSGKTRRYLPAIVREAIRRNVRTLVLAP 1699
DEN1-WP
DEN2-NGC 1650 -NPEIEDDIFRKRKLTIMDLHPGAGKTKRYLPAIVREAIKRGLRTLILAP 1698
         1648 PTPELEEEMFKKRNLTIMDLHPGSGKTRKYLPAIVREAIKRRLRTLILAP 1697
DEN3-H87
                 *....*.*. ********. **.. **.****.. * .***.**
         1698 TRVVAAEMEEALRGLPIRYOTFAVKSEHTGREIVDLMCHATFTTRLLSST 1747
DEN4
DEN1-WP
         1700 TRVVASEMAEALKGMPIRYOTTAVKSEHTGKEIVDLMCHATFTMRLLSPV 1749
DEN2-NGC 1699 TRVVAAEMEEALRGLPIRYQTPAIRAEHTGREIVDLMCHATFTMRLLSPV 1748
DEN3-H87 1698 TRVVAAEMEEAMKGLPIRYQTTATKSEHTGREIVDLMCHATFTMRLLSPV 1747
              ****.** **..*.**** * ..*********** ****
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1748 RVPNYNLIVMDEAHFTDPSSVAARGYISTRVEMGEAAAIFMTATPPGATD 1797
DEN4
         1750 RVPNYNMIIMDEAHFTDPASIAARGYISTRVGMGEAAAIFMTATPPGSVE 1799
DEN1-WP
DEN2-NGC 1749 RVPNYNLIIMDEAHFTDPASIAARGYISTRVEMGEAAGIFMTATPPGSRD 1798
DEN3-H87 1748 RVPNYNLIIMDEAHFTDPASIAARGYISTRVGMGEAAAIFMTATPPGTAD 1797
             1798 PFPQSNSPIEDIEREIPERSWNTGFDWITDYQGKTVWFVPSIKAGNDIAN 1847
DEN4
DEN1-WP
        1800 AFPQSNAVIQDEERDIPERSWNSGYDWITDFPGKTVWFVPSIKSGNDIAN 1849
DEN2-NGC 1799 PFPQSNAPIMDEEREIPERSWSSGHEWVTDFKGKTVWFVPSIKAGNDIAA 1848
        1798 AFPOSNAPIODEERDIPERSWNSGNEWITDFVGKTVWFVPSIKAGNVIAN 1847
DEN3-H87
              ****. * * **.***** .* .*.**. *********
DEN4
         1848 CLRKSGKKVIQLSRKTFDTEYPKTKLTDWDFVVTTDISEMGANFRAGRVI 1897
         1850 CLRKNGKRVVQLSRKTFDTEYQKTKNNDWDYVVTTDISEMGANFRADRVI 1899
DEN1-WP
DEN2-NGC 1849 CLRKNGKKVIQLSRKTFDSEYVKTRTNDWDFVVTTDISEMGANFKAERVI 1898
        1848 CLRKNGKKVIQLSRKTFDTEYQKTKLNDWDFVVTTDISEMGANFIADRVI 1897
DEN3-H87
             1898 DPRRCLKPVILPDGPERVILAGPIPVTPASAAQRRGRIGRNPAQEDDQYV 1947
DEN4
         1900 DPRRCLKPVILKDGPERVILAGPMPVTVASAAQRRGRIGRNQNKEGDQYI 1949
DEN1-WP
DEN2-NGC 1899 DPRRCMKPVILTDGEERVILAGPMPVTHSSAAQRRGRIGRNPKNENDQYI 1948
DEN3-H87 1898 DPRRCLKPVILTDGPERVILAGPMPVTVASAAQRRGRVGRNPQKENDQYI 1947
             ***** **** ** ****** ** . ****** . ***
         1948 FSGDPLKNDEDHAHWTEAKMLLDNIYTPEGIIPTLFGPEREKTQAIDGEF 1997
DEN4
         1950 YMGOPLNNDEDHAHWTEAKMLLDNINTPEGIIPALFEPEREKSAAIDGEY 1999
DEN1-WP
DEN2-NGC 1949 YMGEPLENDEDCAHWKEAKMLLDNINTPEGIIPSMFEPEREKVDAIDGEY 1998
DEN3-H87
         1948 FMGQPLNKDEDHAHWTEAKMLLDNINTPEGIIPALFEPEREKSAAIDGEY 1997
             . * ** *** *** ***** ******
         1998 RLRGEQRKTFVELMRRGDLPVWLSYKVASAGISYKDREWCFTGERNNQIL 2047
DEN4
         2000 RLRGEARKTFVELMRRGDLPVWLSYKVASEGFQYSDRRWCFDGERNNQVL 2049
DEN1-WP
DEN2-NGC 1999 RLRGEARKTFVDLMRRGDLPVWLAYRVAAEGINYADRRWCFDGIKNNQIL 2048
DEN3-H87 1998 RLKGESRKTFVELMRRGDLPVWLAHKVASEGIKYTDRKWCFDGERNNQIL 2047
             DEN4
         2048 EENMEVEIWTREGEKKKLRPRWLDARVYADPMALKDFKEFASGRKSITLD 2097
         2050 EENMDVEIWTKEGERKKLRPRWLDARTYSDPLALREFKEFAAGRRSVSGD 2099
DEN1-WP
         2049 EENVEVEIWTKEGERKKLKPRWLDARIYSDPLTLKEFKEFAAGRKSLTLN 2098
DEN2 - NGC
         2048 EENMDVEIWTKEGEKKKLRPRWLDARTYSDPLALKEFKDFAAGRKSIALD 2097
DEN3-H87
             DEN4
         2098 ILTEIASLPTYLSSRAKLALDNIVMLHTTERGGRAYQHALNELPESLETL 2147.
         2100 LILEIGKLPQHLTQRAQNALDNLVMLHNSEQGGKAYRHAMEELPDTIETL 2149
DEN1-WP
DEN2-NGC 2099 LITEMGRLPTFMTQKARDALDNLAVLHTAEAGGRAYNHALSELPETLETL 2148
         2098 LVTEIGRVPSHLAHRTRNALDNLVMLHTSEHGGRAYRHAVEELPETMETL 2147
DEN3-H87
              2148 MLVALLGAMTAGIFLFFMQGKGIGKLSMGLITIAVASGLLWVAEIQPQWI 2197
DEN4
         2150 MLLALIAVLTGGVTLFFLSGRGLGKTSIGLLCVIASSALLWMASVEPHWI 2199
DEN1-WP
DEN2-NGC 2149 LLLTLLATVTGGIFLFLMSGRGIGKMTLGMCCIITASILLWYAQIQPHWI 2198
DEN3-H87 2148 LLLGLMILLTGGAMLFLISGKGIGKTSIGLICVIASSGMLWMADVPLQWI 2197
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2198 AASIILEFFLMVLLIPEPEKOPTPODNOLIYVILTILTIIGLIAANEMGL 2247
DEN4
DEN1-WP
        2200 AASIILEFFLMVLLIPEPDRQRTPQDNQLAYVVIGLLFMILTAAANEMGL 2249
DEN2-NGC 2199 AASIILEFFLIVLLIPEPEKQRTPQDNQLTYVVIAILTVVAATMANEMGF 2248
DEN3-H87 2198 ASAIVLEFFMMVLLIPEPEKORTPODNOLAYVVIGILTLAAIVAANEMGL 2247
             2248 IEKTKTDFGFY----QVKTETTILDVDLRPASAWTLYAVATTILTPMLRH 2293
DEN4
DEN1-WP
        2250 LETTKKDLGIGHAAAENHHHAAMLDVDLHPASAWTLYAVATTIITPMMRH 2299
DEN2-NGC 2249 LEKTKKDLGLG-SITTQOPESNILDIDLRPASAWTLYAVATTFVTPMLRH 2297
DEN3-H87 2248 LETTKRDLGMS-KEPGVVSPTSYLDVDLHPASAWTLYAVATTVITPMLRH 2296
                               . **.**.******** .***.**
DEN4
        2294 TIENTSANLSLAAIANQAAVLMGLGKGWPLHRMDLGVPLLAMGCYSQVNP 2343
        2300 TIENTTANISLTAIANOAAILMGLDKGWPISKMDIGVPLLALGCYSQVNP 2349
DEN1-WP
DEN2-NGC 2298 SIENSSVNVSLTAIANQATVLMGLGKGWPLSKMDIGVPLLAIGCYSQVNP 2347
DEN3-H87 2297 TIENSTANVSLAAIANQAVVLMGLDKGWPISKMDLGVPLLALGCYSQVNP 2346
             2344 TTLTASLVMLLVHYAIIGPGLQAKATREAQKRTAAGIMKNPTVDGITVID 2393
DEN4
        2350 LTLTAAVFMLVAHYAIIGPGLQAKATREAQKRTAAGIMKNPTVDGIVAID 2399
DEN1-WP
DEN2-NGC 2348 ITLTAALFLLVAHYAIIGPGLQAKATREAQKRAAAGIMKNPTVDGITVID 2397
DEN3-H87 2347 LTLIAAVLLLVTHYAIIGPGLQAKATREAQKRTAAGIMKNPTVDGIMTID 2396
              ** * . . . * . *****************
        2394 LEPISYDPKFEKOLGOVMLLVLCAGOLLLMRTTWAFCEVLTLATGPILTL 2443
DEN4
         2400 LDPVVYDAKFEKQLGQIMLLILCTSQILLMRTTWALCESITLATGPLTTL 2449
DEN1-WP
DEN2-NGC 2398 LDPIPYDPKFEKQLGQVMLLVLCVTQVLMMRTTWALCEALTLATGPISTL 2447
DEN3-H87 2397 LDPVIYDSKFEKQLGQVMLLVLCAVQLLLMRTSWALCEVLTLATGPITTL 2446
             2444 WEGNPGRFWNTTIAVSTANIFRGSYLAGAGLAFSLIKNAQTPRRGTGTTG 2493
DEN4
DEN1-WP
         2450 WEGSPGKFWNTTIAVSMANIFRGSYLAGAGLAFSLMKSLGGGRRGTGAQG 2499
DEN2-NGC 2448 WEGNPGRFWNTTIAVSMANIFRGSYLAGAGLLFSIMKNTTNTRRGTGNIG 2497
DEN3-H87 2447 WEGSPGKFWNTTIAVSMANIFRGSYLAGAGLALSIMKSVGTGKRGTGSQG 2496
                                                   ****
             *** ** ******* ********* * . . *
DEN4
         2494 ETLGEKWKRQLNSLDRKEFEEYKRSGILEVDRTEAKSALKDGSKIKHAVS 2543
         2500 ETLGEKWKRQLNQLSKSEFNTYKRSGIIEVDRSEAKEGLKRGEPTKHAVS 2549
DEN1-WP
DEN2-NGC 2498 ETLGEKWKSRLNALGKSEFQIYKKSGIQEVDRTLAKEGIKRGETDHHAVS 2547
DEN3-H87 2497 ETLGEKWKKKLNQLSRKEFDLYKKSGITEVDRTEAKEGLKRGEITHHAVS 2546
             DEN4
         2544 RGSSKIRWIVERGMVKPKGKVVDLGCGRGGWSYYMATLKNVTEVKGYTKG 2593
         2550 RGTAKLRWFVERNLVKPEGKVIDLGCGRGGWSYYCAGLKKVTEVKGYTKG 2599
DEN1-WP
DEN2-NGC 2548 RGSAKLRWFVERNMVTPEGKVVDLGCGRGGWSYYCGGLKNVREVKGLTKG 2597
         2547 RGSAKLOWFVERNMVIPEGRVIDLGCGRGGWSYYCAGLKKVTEVRGYTKG 2596
DEN3-H87
             2594 GPGHEEPIPMATYGWNLVKLHSGVDVFYKPTEQVDTLLCDIGESSSNPTI 2643
DEN4
         2600 GPGHEEPIPMATYGWNLVKLYSGKDVFFTPPEKCDTLLCDIGESSPNPTI 2649
DEN1-WP
DEN2-NGC 2598 GPGHEEPIPMSTYGWNLVRLQSGVDVFFTPPEKCDTLLCDIGESSPNPTV 2647
DEN3-H87 2597 GPGHEEPVPMSTYGWNIVKLMSGKDVFYLPPEKCDTLLCDIGESSPSPTV 2646
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2644 EEGRTLRVLKMVEPWLSSKPEFCIKVLNPYMPTVIEELEKLQRKHGGNLV 2693
DEN4
         2650 EEGRTLRVLKMVEPWLRGN-QFCIKILNPYMPSVVETLEQMQRKHGGMLV 2698
DEN1-WP
DEN2-NGC 2648 EAGRTLRVLNLVENWLNNNTQFCIKVLNPYMPSVIEKMEALQRKYGGALV 2697
DEN3-H87 2647 BESRTIRVLKMVEPWLKNN-QFCIKVLNPYMPTVIEHLERLQRKHGGMLV 2695
                               _ **** ***** * * * *** ** **
        2694 RCPLSRNSTHEMYWVSGASGNIVSSVNTTSKMLLNRFTTRHRKPTYEKDV 2743
DEN4
        2699 RNPLSRNSTHEMYWVSCGTGNIVSAVNMTSRMLLNRFTMAHRKPTYERDV 2748
DEN1-WP
DEN2-NGC 2698 RNPLSRNSTHEMYWVSNASGNIVSSVNMISRMLINRFTMRHKKATYEPDV 2747
DEN3-H87 2696 RNPLSRNSTHEMYWISNGTGNIVSSVNMVSRLLLNRFTMTHRRPTIEKDV 2745
             2744 DLGAGTRSVSTETEKPDMTIIGRRLQRLQEEHKETWHYDQENPYRTWAYH 2793
DEN4
DEN1-WP
         2749 DLGAGTRHVAVEPEVANLDIIGQRIENIKNGHKSTWHYDEDNPYKTWAYH 2798
DEN2-NGC 2748 DLGSGTRNIGIESEIPNLDIIGKRIEKIKQEHETSWHYDQDHPYKTWAYH 2797
DEN3-H87 2746 DLGAGTRHVNAEPETPNMDVIGERIKRIKEEHSSTWHYDDENPYKTWAYH 2795
             2794 GSYEAPSTGSASSMVNGVVKLLTKPWDVIPMVTQLAMTDTTPFGQQRVFK 2843
DEN4
         2799 GSYEVKPSGSASSMVNGVVRLLTKPWDVIPMVTQIAMTDTTPFGQQRVFK 2848
DEN1-WP
DEN2-NGC 2798 GSYETKQTGSASSMVNGVVRLLTKPWDVVPMVTQMAMTDTTPFGQQRVFK 2847
DEN3-H87 2796 GSYEVKATGSASSMINGVVKLLTKPWDVVPMVTOMAMTDTTPFGOORVFK 2845
                   2844 EKVDTRTPOPKPGTRMVMTTTANWLWALLGKKKNPRLCTREEFISKVRSN 2893
DEN4
         2849 EKVDTRTPKAKRGTAQIMEVTARWLWGFLSRNKKPRICTREEFTRKVRSN 2898
DEN1-WP
DEN2-NGC 2848 EKVDTRTOEPKEGTKKLMKITAEWLWKELGKKKTPRMCTREEFTRKVRSN 2897
         2846 EKVDTRTPRPMPGTRKVMEITAEWLWRTLGRNKRPRLCTREEFTKKVRTN 2895
DEN3-H87
                           _ * ** *** * . * **.**** ***.*
         2894 AAIGAVFQEEQGWTSASEAVNDSRFWELVDKERALHQEGKCESCVYNMMG 2943
DEN4
         2899 AAIGAVFVDENOWNSAKEAVEDERFWDLVHRERELHKQGKCATCVYNMMG 2948
DEN1-WP
DEN2-NGC 2898 AALGAIFTDENKWKSAREAVEDSRFWELVDKERNLHLEGKCETCVYNMMG 2947
DEN3-H87 2896 AAMGAVFTEENOWDSARAAVEDEEFWKLVDRERELHKLGKCGSCVYNMMG 2945
             **.**. * . * ** ** ** ** ** **
         2944 KREKKLGEFGRAKGSRAIWYMWLGARFLEFEALGFLNEDHWFGRENSWSG 2993
DEN4
DEN1-WP
         2949 KREKKLGEFGKAKGSRAIWYMWLGARFLEFEALGFMNEDHWFSRENSLSG 2998
DEN2-NGC 2948 KREKKLGEFGKAKGSRAIWYMWLGARFLEFEALGFLNEDHWFSRENSLSG 2997
DEN3-H87 2946 KREKKLGEFGKAKGSRAIWYMWLGARYLEFEALGFLNEDHWFSRENSYSG 2995
             ******* *** ***** *** *** *** *** *** **
DEN4
         2994 VEGEGLHRLGYILEEIDKKDGDLMYADDTAGWDTRITEDDLQNEELITEQ 3043
         2999 VEGEGLHKLGYILRDISKIPGGNMYADDTAGWDTRITEDDLONEAKITDI 3048
DEN1-WP
DEN2-NGC 2998 VEGEGLHKLGYILRDVSKKEGGAMYADDTAGWDTRITLEDLKNEEMVTNH 3047
DEN3-H87 2996 VEGEGLHKLGYILRDISKIPGGAMYADDTAGWDTRITEDDLHNEEKITQQ 3045
              3044 MAPHHKILAKAIFKLTYONKVVKVLRPTPRGAVMDIISRKDQRGSGQVGT 3093
DEN4
         3049 MEPEHALLATSIFKLTYQNKVVRVQRPAKNGTVMDVISRRDQRGSGQVGT 3098
DEN1-WP
DEN2-NGC 3048 MEGEHKKLAEAIFKLTYQNKVVRVQRPTPRGTVMDIISRRDQRGSGQVGT 3097
DEN3-H87 3046 MDPEHROLANAIFKLTYONKVVKVQRPTPKGTVMDIISRKDQRGSGQVGT 3095
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3094 YGLNTFTNMEVQLIRQMEAEGVITQDDMQNPKGLKERVEKWLKECGVDRL 3143
DEN1-WP
        3099 YGLNTFTNMEAQLIRQMESEGIFSPSELETPN-LAERVLDWLKKHGTERL 3147
DEN2-NGC 3098 YGLNTFTNMEAQLIRQMEGEGVFKSIQHLTVT-EEIAVQNWLARVGRERL 3146
DEN3-H87 3096 YGLNTFTNMEAQLIRQMEGEGVLSKADLENPHPLEKKITQWLETKGVERL 3145
             ******* *****
        3144 KRMAISGDDCVVKPLDERFGTSLLFLNDMGKVRKDIPQWEPSKGWKNWQE 3193
DEN4
DEN1-WP
        3148 KRMAISGDDCVVKPIDDRFATALTALNDMGKVRKDIPQWEPSKGWNDWQQ 3197
DEN2-NGC 3147 SRMAISGDDCVVKPLDDRFASALTALNDMGKVRKDIQQWEPSRGWNDWTQ 3196
DEN3-H87 3146 KRMAISGDDCVVKPIDDRFANALLALNDMGKVRKDIPQWQPSKGWHDWQQ 3195
              3194 VPFCSHHFHKIFMKDGRSLVVPCRNQDELIGRARISQGAGWSLRETACLG 3243
DEN4
DEN1-WP
        3198 VPFCSHHFHQLIMKDGREIVVPCRNQDELVGRARVSQGAGWSLRETACLG 3247
DEN2-NGC 3197 VPFCSHHFHELIMKDGRVLVVPCRNODELIGRARISQGAGWSLRETACLG 3246
DEN3-H87 3196 VPFCSHHFHELIMKDGRKLVVPCRPODELIGRARISOGAGWSLRETACLG 3245
             *******
        3244 KAYAQMWSLMYFHRRDLRLASMAICSAVPTEWFPTSRTTWSIHAHHQWMT 3293
DEN4
        3248 KSYAQMWQLMYFHRRDLRLAANAICSAVPVDWVPTSRTTWSIHAHHQWMT 3297
DEN1-WP
DEN2-NGC 3247 KSYAQMWSLMYFHRRDLRLAANAICSAVPSHWVPTSRTTWSIHAKHEWMT 3296
DEN3-H87 3246 KAYAQMWTLMYFHRRDLRLASNAICSAVPVHWVPTSRTTWSIHAHHQWMT 3295
             DEN4
        3294 TEDMLKVWNRVWIEDNPNMTDKTPVHSWEDIPYLGKREDLWCGSLIGLSS 3343
        3298 TEDMLSVWNRVWIEENPWMEDKTHVSSWEDVPYLGKREDRWCGSLIGLTA 3347
DEN1-WP
DEN2-NGC 3297 TEDMLTVWNRVWIOENPWMEDKTPVESWEEIPYLGKREDQWCGSLIGLTS 3346
DEN3-H87 3296 TEDMLTVWNRVWIEDNPWMEDKTPVTTWEDVPYLGKREDQWCGSLIGLTS 3345
             3344 RATWAKNIHTAITQVRNLIGKEEYVDYMPVMKRYSAPSESEGVL 3387
DEN4
DEN1-WP
        3348 RATWATNIOVAINOVRRLIGNENYLDFMTSMKRFKNESDPEGALW 3392
DEN2-NGC 3347 RATWAKNIQTAINQVRSLIGNEEYTDYMPSMKRFRREEEEAGVLW 3391
DEN3-H87 3346 RATWAQNILTAIQQVRSLIGNEEFLDYMPSMKRFRKEEESEGAIW 3390
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<sup>\*</sup> Residue identity

<sup>.</sup> Residue similarity

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[0238] While the present invention has been described in some detail for purposes of clarity and understanding, one skilled in the art will appreciate that various changes in form and detail can be made without departing from the true scope of the invention. All figures, tables, and appendices, as well as patents, applications, and publications, referred to above, are hereby incorporated by reference.